REMARKS

Reconsideration and reexamination of the subject application are respectfully requested in light of the foregoing amendments and following remarks. The amendments are made without prejudice or disclaimer of Applicants' right to claim any subject matter disclosed in the specification in a subsequently filed continuing application.

1. Status of the Claims

Claims 1-31 are pending. Claims 3-6, 10-12, and 16-31 are withdrawn from consideration. Claims 1, 2, 7-9, and 13-15 are rejected. Claim 31 is canceled by entry of the present amendment.

2. Notice of Prosecution in Another Application

Applicants direct the Office's attention to Application Serial No. 10/827,839 ("the '839 application"), directed in part to a method of lowering body temperature in an individual, comprising administration of an effective amount of at least one compound according to Formula I, where the administered compounds according to Formula I comprise an (*R*)-enantiomer, substantially free of the corresponding (*S*)-enantiomer.

An Office Action was mailed December 29, 2007, in the '839 application. The Office Action cites the instant application in a provisional rejection under the judicially created doctrine of obviousness type double patenting. The Office Action further cites U.S. Patent No. 6,080,736 ("Landry"), which also is cited in the instant Office Action. The Office Action also cites ZETHOF *et al.*, "Stress-induced hyperthermia as a putative anxiety model," *Eur. J. Pharm.* 294: 125-35 (1995), Elsevier, Amsterdam, Holland ("Zethof") in a rejection. Zethof is cited in an IDS filed concurrently with the instant response.

3. Acceptance of the Drawings

Applicants appreciate the indication that the drawings filed February 17, 2004 are acceptable.

4. **Requirement for Restriction/Election**

Applicants appreciate the indication that claim 1 is a linking claim that links inventions I(a) and I(b) (collectively, claims 1-30). Applicants request timely rejoinder of withdrawn claims 3-6, 10-12, and 16-30 pursuant to 37 C.F.R. § 1.104. Withdrawn claim 31 is canceled.

5. **Rejection under 35 U.S.C. § 112, Second Paragraph**

Claims 1, 2, 7-9, and 13-15 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants traverse the rejection.

The Office alleges that "substantially" is a relative term that renders claim 1 indefinite. It is well established that "the definiteness of the language employed must be analyzed—not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore* , 439 F.2d 1232, 1235, 169 U.S.P.Q. 236, 238 (C.C.P.A. 1971). In particular, Applicants can use whatever terms they choose in the claims so long as any special meaning assigned to a term is clearly set forth in the specification. *See* M.P.E.P., 8th ed., revised Sept. 2007 (MPEP) § 2173.01.

In the present case, "substantially" must be interpreted in light of the teachings of the specification at page 19, line 19, through page 20, line 4. The specification states, for example:

> The term "substantially isolated," or "substantially free of the other enantiomer" . . . means the (*R*)- and (*S*)-enantiomers of the compound have been separated such that the composition is 80% or more by weight a single enantiomer.

From this definition, the artisan of ordinary skill in the relevant art would understand what is meant by "substantially" in the claims. Accordingly, the claim terms are definite, and the rejection should be withdrawn.

6. **Rejection under 35 U.S.C. § 102(b)**

Claims 1, 2, 7, and 8 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Ito *et al.*, *Iyakuhin Kenkyu* 12: 587-600 (1981) ("Ito"). Applicants traverse the rejection.

The Office alleges that Ito anticipates the claims based solely on the Office's interpretation of the claims as encompassing a 50:50 racemic mixture of (*R*)- and (*S*)-enantiomers of tofisopam. For the reasons set forth above, the claims are not directed to a 50:50 racemic mixture. Anticipation rejections may not be based on improperly and overly broadly interpreted claim terms. *In re Buszard*, 84 U.S.P.Q.2d 1749, 1751 (Fed. Cir. 2007). Ito does not teach administered compounds according to Formula I comprising an (*S*)-enantiomer, substantially free of the corresponding (*R*)-enantiomer. Ito thus does not teach all the elements of the claimed invention. Accordingly, Ito does not anticipate the claims, and the rejection should be withdrawn.

7. **Rejection under 35 U.S.C. § 103**

Claims 1, 2, 7-9, and 13-15 are rejected under 35 U.S.C. § 103 as allegedly obvious over U.S. Patent No. 6,080,736 ("Landry"). Applicants traverse the rejection.

The legal standard of obviousness

The Office alleges that the claims are obvious because Landry teaches that optically pure tofisopam enantiomers exert different biological effects, and that one of those effects relates to hot flashes associated with panic disorders. Office Action, page 6. Whether a claim is obvious is based on an objective analysis of (1) the scope and content of the prior art, (2) the differences between the prior art and each element of the claimed invention, (3) the level of skill in the pertinent art, and (4) objective evidence of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 15-17 (1966); *see also* M.P.E.P. § 804.

With particular regard to the determination of obviousness of chemical compounds, the Federal Circuit recently held: "[The] test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*." *Takeda Chem. Indus. Ltd. v. Alphapharm Pty. Ltd.*, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007). The appropriate test is whether "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness." *In re Dillon*, 919 F.2d 688, 16 U.S.P.Q.2d 1897, 1901 (*en banc*) (Fed. Cir. 1990). That is, in addition to structural similarity between the compounds, a prima facie case of obviousness requires a showing of

"adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32, 226 U.S.P.Q. 870, 872 (Fed. Cir. 1985). The prior art must suggest the specific molecular modifications necessary to achieve the claimed invention. *Takeda*, 83 U.S.P.Q.2d at 1174 (citing cases).

Analysis of the *Graham* factors

In the present case, the claims are directed in part to a method of lowering body temperature in an individual, comprising administering an effective amount of at least one compound according to Formula I, where the compound comprises an ***(S)-enantiomer*** that is substantially free of the corresponding (*R*)-enantiomer. In one embodiment, the treated individual is afflicted with a disorder associated with an elevated body temperature, where the disorder comprises hot flashes.

By contrast, Landry discloses methods of using the ***(R)-enantiomer*** of tofisopam to treat anxiety disorders. Landry teaches that the physical difference between enantiomers "is of profound importance in nature" (col. 1, lines 64-66) and that "enantiomers of a given drug may have markedly different properties in a biological system" (col. 2, lines 17-19). Landry further states (col. 2, lines 42-46):

> The effect of chirality on drug action is complex and may involve any or all systems in the body which are capable of reacting to a chiral molecule in an asymmetric or enantioselective manner.

Landry suggests that enantiomers of tofisopam, like other chiral molecules, may show different biological activities (col. 9, lines 1-6), but that the state of the art was not sufficiently advanced to reveal which "unexpected properties" were possessed by (*R*)-tofisopam (col. 9, lines 6-11). Landry discloses that (*R*)-tofisopam yields unexpectedly superior results in treating anxiety disorders (col. 13, lines 42-49; emphasis added):

> The invention encompasses the use of R-tofisopam or an R-tofisopam composition in the treatment of anxiety and anxiety disorders. Thus, one embodiment of the present invention relates to the treatment of anxiety and anxiety disorders by the administration of a therapeutically effective amount of R-tofisopam or a pharmaceutically acceptable salt thereof, which has ***unexpectedly better activity than*** its racemate and ***S-tofisopam***.

In the middle of a lengthy discussion on the use of tofisopam in treating anxiety-related disorders (col. 7, line 35, through col. 13, line 32), Landry mentions the use of

tofisopam in treating panic attacks, which are marked by a wide variety of symptoms, such as "chills or hot flashes." Landry, col. 9, line 47. Landry does not disclose whether this activity is an unexpected property of the (*R*)- or (*S*)-enantiomer of tofisopam.

Viewing Landry as a whole, the artisan of ordinary skill arguably would use (*R*)-tofisopam to treat anxiety disorders, based on the unexpectedly better activity of (*R*)-tofisopam over (*S*)-tofisopam. The claimed method, however, comprises administering an effective amount of at least one compound according to Formula I, where compounds comprise an (*S*)-enantiomer that is substantially free of the corresponding (*R*)-enantiomer, to lower body temperature. Landry does not teach or suggest at least the claim element of an (*S*)-enantiomer that is substantially free of the corresponding (*R*)-enantiomer. Because of the unpredictability in this art, the artisan would not have had a reasonable expectation of successfully modifying Landry to carry out the claimed methods with a compound substantially free of the (*R*)-enantiomer. Absent sufficient support or motivation provided by the prior art to make the proposed modification to Landry, the claims are non-obviousness over Landry. *See Dillon*, 16 U.S.P.Q.2d at 1901; *Grabiak*, 226 U.S.P.Q. at 872; *Takeda*, 83 U.S.P.Q.2d at 1174. Accordingly, the rejection should be withdrawn.

Because the claimed methods use compounds comprising an (*S*)-enantiomer that is substantially free of the corresponding (*R*)-enantiomer, it is irrelevant whether Landry would have rendered obvious a method of lowering body temperature of an individual, comprising administering to the individual an effective amount of racemic tofisopam or (*R*)-tofisopam. Applicants herein neither expressly nor impliedly disclaim any subject matter related to racemic tofisopam or (*R*)-tofisopam in this regard.

8. Rejections under the Judicially Created Doctrine of Obviousness Type Double Patenting

Application Serial No. 10/827,839

Claims 1, 2, 7-9, and 13-15 are provisionally rejected under the doctrine of obviousness type double patenting over claims 1-29 and 31 of co-pending Application Serial No. 10/827,839 ("the '839 application"). Applicants traverse the rejection.

The instant claims are directed to a method comprising the use of compounds according to Formula I, where the compound comprises an ***(S)-enantiomer*** substantially free of the corresponding (*R*)-enantiomer. By contrast, the cited claims of the '839 application are directed to a method comprising the use of compounds according to Formula I, where the compound comprises an ***(R)-enantiomer*** substantially free of the corresponding (*S*)-enantiomer.

As set forth above, the test for obviousness is whether "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness." *Dillon*, 16 U.S.P.Q.2d at 1901 ; *see also Grabiak*, 226 U.S.P.Q. at 872; *Takeda*, 83 U.S.P.Q.2d at 1174. The Office has provided no evidence from the '839 application claims, alone or in combination with prior art, to support a modification of the '839 application claims to arrive at the instantly claimed invention. Absent such support, the instant claims are non-obvious over the '839 application claims, and the provisional rejection is improper. The rejection accordingly should be withdrawn.

U.S. Patent No. 6,649,607

Claims 1, 2, 7-9, and 13-15 are rejected under the doctrine of obviousness type double patenting over claims 7-22 of U.S. Patent No. 6,649,607 ("the '607 patent"). The Office inadvertently mischaracterizes this rejection as a provisional rejection. Applicants traverse the rejection.

The Office alleges that the '607 patent claims inherently anticipate the instant claims. On this basis, the Office alleges that it would have been obvious to modify the '607 patent claims to arrive at the instant claims. The Office confuses the proper grounds for a rejection under the judicially created doctrine of obviousness type double patenting. Obviousness type double patenting is not based on inherent anticipation. Nevertheless, Applicants respond to both prongs of the rejection for the sake of completeness.

The Office has not made a *prima facie* case of inherent anticipation. The '607 patent claims are directed to a method of treating convulsions or seizures (claim 7) or treating a subject at risk of suffering from a convulsion or seizure (claim 8). The therapeutic

compositions recited in the '607 patent claims are delivered to different individuals, i.e., subjects at risk of suffering from convulsions or seizures. There is no more than a possibility or probability that such patients also are in need of a method of lowering body temperature, as instantly recited. Inherent anticipation cannot be based on possibilities or probabilities. *See, e.g., In re Oelrich*, 666 F.2d 578, 581-82 (C.C.P.A. 1981). For this reason alone, the '607 patent claims do not anticipate the instant claims.

Nor has the Office made a *prima facie* case of obviousness. To the extent that the Office bases the present rejection on inherency, the rejection is improper and should be withdrawn on this basis alone. It is axiomatic that an inherent property of a compound that is unappreciated by the artisan is irrelevant to the determination of obviousness. *See, e.g., In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.").

Further, the Office provides no evidence from the '607 patent claims, alone or combined with the prior art, to support a modification of the '607 patent claims to arrive at the instantly claimed invention. In particular, the Office has not explained why treatment of convulsions or seizures would suggest a method of lowering body temperature. The Office instead merely provides a conclusory remark that it would. It is well established that obviousness cannot be based on conclusory remarks. *See, e.g., KSR Int'l Co. v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, 1396 (2007); *In re Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002). For all these reasons, the rejection is improper and should be withdrawn.

CONCLUSION

In conclusion, this amendment and reply is believed to be a full response to the outstanding Office Action. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0573. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is respectfully requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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BY: _____

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